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Cardiac Imaging

Usefulness of Fluorine-18 Positron Emission Tomography/Computed Tomography for Identification of Cardiovascular Implantable Electronic Device Infections

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Objectives This study evaluated the usefulness of fluorodesoxyglucose marked by fluorine-18 (^{18}F-FDG) positron emission tomography (PET) and computed tomography (CT) in patients with suspected cardiovascular implantable electronic device (CIED) infection.

Background CIED infection is sometimes challenging to diagnose. Because extraction is associated with significant morbidity/mortality, new imaging modalities to confirm the infection and its dissemination would be of clinical value.

Methods Three groups were compared. In Group A, 42 patients with suspected CIED infection underwent ^{18}F-FDG PET/CT. Positive PET/CT was defined as abnormal uptake along cardiac devices. Group B included 12 patients without infection who underwent PET/CT 4 to 8 weeks post-implant. Group C included 12 patients implanted for >6 months without infection who underwent PET/CT for another indication. Semi-quantitative ratio (SQR) was obtained from the ratio between maximal uptake and lung parenchyma uptake.

Results In Group A, 32 of 42 patients with suspected CIED infection had positive PET/CT. Twenty-four patients with positive PET/CT underwent extraction with excellent correlation. In 7 patients with positive PET/CT, 6 were treated as superficial infection with clinical resolution. One patient with positive PET/CT but negative leukocyte scan was considered false positive due to Dacron pouch. Ten patients with negative-PET/CT were treated with antibiotics and none has relapsed at 12.9 ± 1.9 months. In Group B, patients had mild uptake seen at the level of the connector. There was no abnormal uptake in Group C patients. Median SQR was significantly higher in Group A (A = 2.02 vs. B = 1.08 vs. C = 0.57; $p < 0.001$).

Conclusions PET/CT is useful in differentiating between CIED infection and recent post-implant changes. It may guide appropriate therapy. (J Am Coll Cardiol 2012;59:1616–25) © 2012 by the American College of Cardiology Foundation

Cardiovascular implantable electronic device (CIED) infection is one of the most feared complications of device implantation. The incidence of CIED infections is 1.9 cases by 1,000 implants/year (1,2). The total number of CIED infections is increasing, mainly with new clinical indications and the growing number of implants worldwide (3). Definitive CIED infection diagnosis is often challenging. In addition, CIED infection treatment can be invasive, requiring complete extraction of the generator and all leads. Lead extraction is associated with significant morbidity (major complications = 1.5% to 2%) and mortality (0.8%) (4,5). New imaging modalities to confirm the infectious process and its dissemination would be of clinical value.

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Combined fluorodesoxyglucose marked by fluorine-18 (^{18}F-FDG) positron emission tomography (PET) and computed tomography (CT) is a well-established imaging modality that allows 3-D measurement of metabolic activity within an organ obtained from the emission of positrons following disintegration of an injected radioactive product. The value of ^{18}F-FDG PET/CT is already recognized in oncology for cancer diagnosis and staging, and in cardiology

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to assess myocardial viability. ^{18}F-FDG PET/CT is also used for infection detection associated with vascular or orthopedic prostheses (6–9). There are few case reports (10–13) and only 2 small pilot studies (14,15) in the literature where ^{18}F-FDG PET/CT has been used for CIED infection diagnosis. ^{18}F-FDG PET/CT appears as an interesting adjunct for CIED infection diagnosis because it allows the use of ^{18}F-FDG as a marker. This is a glucose analogue, which is incorporated and retained within the cells with higher metabolic activity. It might help the clinician to confirm the diagnosis of CIED infection, determine the systemic extension of the infectious process, and justify an invasive procedure.

The goal of this study was first to evaluate the usefulness of ^{18}F-FDG PET/CT for the detection of CIED infections. Secondly, because there is sometimes a real clinical challenge to diagnose a CIED infection or superficial skin infection or inflammation in recent post-implant patients, we tested a group of patients with recent implants and no clinical suspicion of infection to assess their "baseline" ^{18}F-FDG uptake level.

Methods

The protocol was approved by the Ethics Committee from the Institut universitaire de cardiologie et pneumologie de Quebec.

Three groups of consecutive patients were prospectively compared. The first group (Group A = suspected CIED infection) included patients with clinically suspected CIED infections (n = 42). CIED infection was defined by the presence of 1 of the following (5,16): 1) pocket infection = local signs of inflammation at the generator pocket, including erythema, warmth, fluctuance, wound dehiscence, tenderness, or purulent drainage (n = 26); 2) device erosion = cutaneous erosion with percutaneous exposure of the generator and/or leads (n = 6); 3) lead endocarditis = mass adherent to a lead in a patient with positive blood cultures or other suggestive features for infection or lead tip cultures (n = 7); and 4) persistent or recurrent bacteremia in the absence of another identifiable source (n = 3).

Treatment decisions were on the basis of the degree of certainty of the CIED infection diagnosis, results of conventional tests, and clinical guidelines (5). Results of the ^{18}F-FDG PET/CT were transmitted to the treating physicians, but the exam was only complementary and never used alone for the final decision on the management of these patients. Extraction was performed when deep CIED infection (i.e., infection involving the generator and/or the leads) was suspected. The second group (Group B = controls: acute phase) included patients with recent device implantation but without signs of infection in order to know the background residual inflammation at 4 to 8 weeks post-implant (n = 12), the period where the diagnosis can be more challenging. These patients were recruited at the time of their first follow-up visit approximately 1 month post-implant. Finally, the third group (Group C = controls: chronic phase) included patients with remote device implantation (>6 months) without signs of infection who underwent ^{18}F-FDG PET/CT for another indication (n = 12).

Clinical data were collected from all patients, including blood work (white blood cell count, neutrophils count, C-reactive protein level, and blood cultures if available). A clinical correlation was performed in patients who had a transesophageal echocardiogram (TEE) and/or extraction in addition to ^{18}F-FDG PET/CT.

Abbreviations and Acronyms

^{18}F-FDG = fluorodesoxyglucose marked by fluorine-18

CIED = cardiovascular implantable electronic device

CT = computed tomography

LVEF = left ventricular ejection fraction

PET = positron emission tomography

ROC = receiver-operating characteristic

TEE = transesophageal echocardiogram

^{18}F-FDG PET/CT. All patients underwent ^{18}F-FDG PET/CT (GE Discovery PET/CT, GE Healthcare, Piscataway, New Jersey) after an 8-h fasting period. PET imaging was performed 65 ± 17 min after injection of 8.1 ± 1.8 mCi of FDG (equivalent to 293.1 ± 74.4 MBq). Simultaneously, a low-dose CT without intravenous contrast but with gastric opacification was obtained for attenuation correction and anatomic localization. The capillary glucose was measured at the time of the injection. Limited imaging to the torso and superior abdomen was performed in Group B to limit radiation exposure.

Each case was reviewed by 2 experienced nuclear physicians. Discordant analyses were resolved by consensus. The analysis was performed using MIMvista software (MIM Software Inc., Cleveland, Ohio). Both attenuation-corrected as well as non–attenuation-corrected images were reviewed in order to recognize artifacts related to the correction of attenuation in proximity of an object of high density (e.g., metal of generator), but only the non–attenuation-corrected images were used for final interpretation. A positive ^{18}F-FDG PET/CT was defined as an abnormal ^{18}F-FDG uptake near the generator pocket and/or along the CIED (i.e., generator or leads). Sites of abnormal ^{18}F-FDG uptakes were noted as well as the site of maximal ^{18}F-FDG uptakes. Sites of abnormal ^{18}F-FDG uptakes were separated by areas: skin (superficial), subcutaneous tissue, surrounding of generator, overlying leads, and intravascular/intracardiac. A qualitative visual score was noted: none (score = 0), mild hypermetabolism (equal or less to lung parenchyma; score = 1), moderate hypermetabolism (more intense than lung parenchyma; score = 2), and severe hypermetabolism (very intense uptake; score = 3). There was interobserver agreement for the qualitative visual score as well as for the final PET/CT conclusion on whether or not CIED infection was present. A semi-quantitative ratio was also collected from non–attenuation-corrected images. A ratio was created between the maximum count

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rate of the device over a mean count rate between normal right and left lung parenchyma. Areas of abnormal lung parenchyma were avoided. Other zones of captation were avoided (skin, shoulder, thyroid gland). Values for the semi-quantitative ratio were measured on at least 2 separate occasions with excellent reproducibility.

Statistical analysis. Data were expressed using the mean ± SD or the median (interquartile range) for continuous variables or as percentage for categorical data. The analyses of categorical variables were performed using a generalized linear model with a binary distribution function for the dependant variable. For continuous data, a 1-way analysis of variance was fitted to compare groups with heterogeneous variances and whether the model could be reduced to a 1-way analysis with the same variance across groups was tested. For the time since last intervention and semi-quantitative ratio, values were log transformed to stabilize variances. Reported p values are on the basis of these transformations. A posteriori comparisons were performed using Tukey's comparison technique. The univariate normality assumptions were verified with the Shapiro-Wilk test. Sensibility and specificity values of ^{18}F-FDG PET/

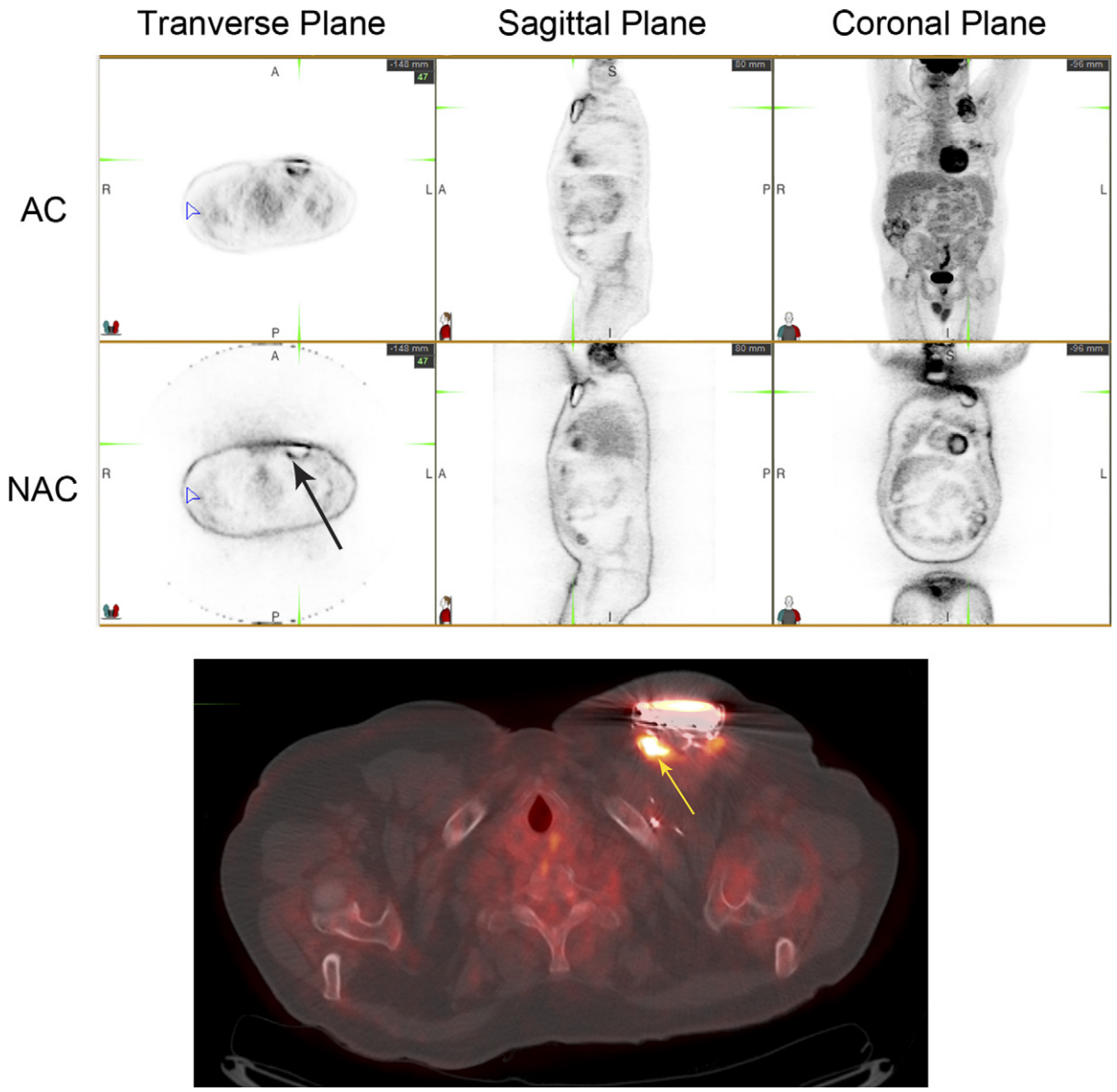

Figure 1 CIED Infection in a Patient With a Deep Pocket Infection and Positive ^{18}F-FDG PET/CT (Group A)

(Upper panels) Attenuation-corrected (AC) and non–attenuation-corrected (NAC) images of the fluorodesoxyglucose marked by fluorine-18 (^{18}F-FDG) positron emission tomography (PET) in different planes shows abnormal uptake seen posterior to the generator **(black arrow)** and compatible with cardiovascular implantable electronic device (CIED) infection. **(Lower panel)** The same abnormality on a fused ^{18}F-FDG PET/computed tomography (CT) **(yellow arrow)**. A = anterior, L = left; P = posterior; R = right.

CT, on the basis of the qualitative visual score, were assessed in comparison with the actual gold standard, which is the clinical definition of CIED infection mentioned previously. A receiver operating characteristic (ROC) curve was calculated from the semi-quantitative ratio. A Pearson correlation test was performed between ^{18}F-FDG PET/CT results and clinical findings at the time of the extraction. The results were considered significant with p values ≤0.05. All analyses were conducted using the statistical package SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Patient characteristics. Group A included 42 patients with suspected CIED infection, on the basis of history, physical examination, and initial blood tests. This group

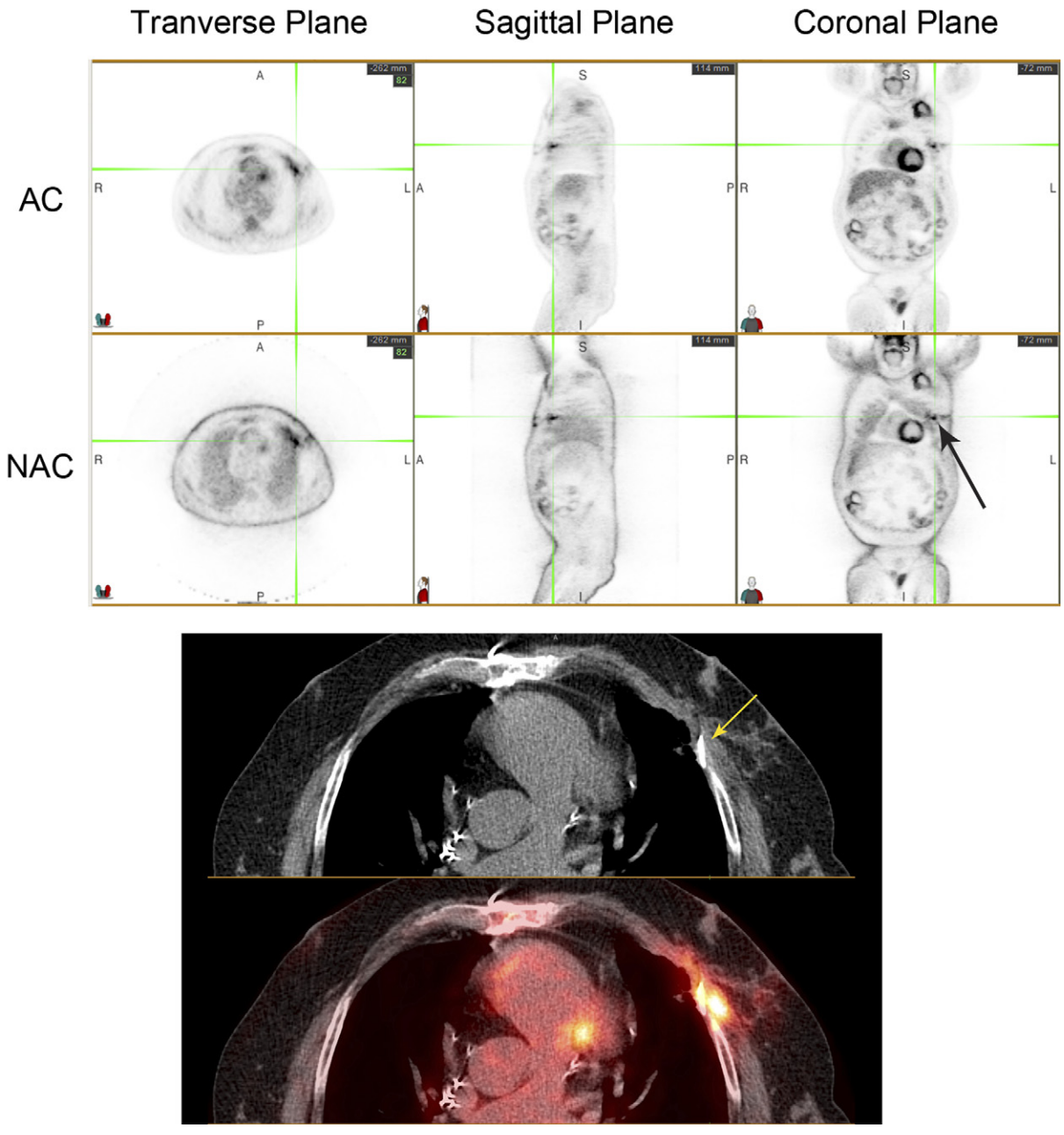

Figure 2 Cardiovascular Implantable Electronic Device Infection in a Patient With an Infected Epicardial Lead and Positive ^{18}F-FDG PET/CT (Group A)

(Upper panels) AC and NAC images of the ^{18}F-FDG PET in different planes shows abnormal uptake seen along the course of the epicardial lead **(black arrow)**. **(Lower panel)** Two images of the same CT transverse section demonstrating abnormal uptake on the lead with ^{18}F-FDG PET fusion **(lower component)** and the corresponding plain CT for lead localization **(upper component)** (**yellow arrow** = epicardial lead). Abbreviations as in Figure 1.

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comprised 28 men and 14 women with a mean age of 62 ± 17 years, and a mean left ventricular ejection fraction (LVEF) of 44 ± 17% (Table 1). All patients underwent ^{18}F-FDG PET/CT for risk stratification, and several patients also had a TEE (n = 22). The main presenting symptom or sign was local wound infection (n = 16), pre-erosion/erosion (n = 13), bacteremia (n = 10), fever of unknown origin (n = 1), local persistent swelling (n = 1), and chronic wound discomfort (n = 1). Eight patients without local signs of device infection met the Duke criteria for infective endocarditis. Twenty-four patients underwent extraction and 18 patients were treated with antibiotics only. After complete evaluation, 35 patients had confirmed CIED infections. In the remaining 7 patients, 5 patients were treated successfully for an infection unrelated to their cardiac device, 1 patient with fever of unknown origin was finally diagnosed with reactive arthritis, and 1 patient previously treated for superficial infection but now with chronic local discomfort had no evidence of recurrent infection after extensive work-up.

In Group B (controls: acute phase), 12 patients without signs of infection were enrolled between 4 and 8 weeks post-implant to undergo ^{18}F-FDG PET/CT in order to obtain background residual inflammation early post-procedure. It included 11 men and 1 woman with a mean age of 65 ± 8 years and a mean LVEF of 39 ± 13%. The ^{18}F-FDG PET/CT was performed at a median of 1.3 months after the patients' last cardiac device operation.

Group C (controls: chronic phase) comprised 12 patients with implanted devices for at least 6 months without any sign of CIED infection who underwent ^{18}F-FDG PET/CT for another indication (work-up of lung nodule = 8, cancer

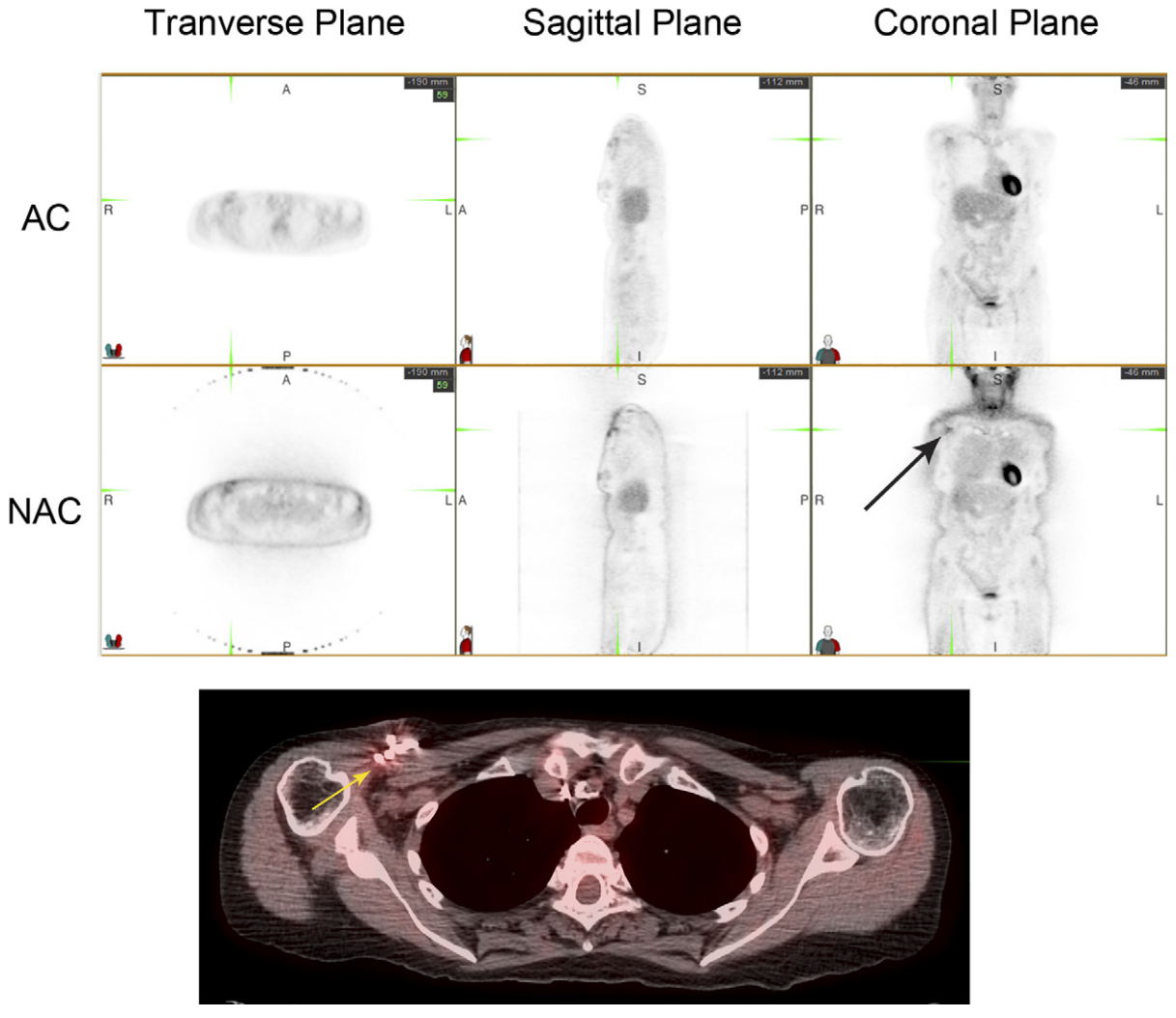

Figure 3 **Recent Post-Implantation Changes on ^{18}F-FDG PET/CT in a Patient 6 Weeks Post–Device Implantation (Group B)**

(Upper panels) AC and NAC images of the ^{18}F-FDG PET in different planes shows mild residual uptake at the level of the connector on the right pre-pectoral area **(black arrow)**. **(Lower panel)** The same result on a fused ^{18}F-FDG PET/CT **(yellow arrow)**. Abbreviations as in Figure 1.

staging = 2, chronic cough = 1, pre-transplantation evaluation = 1). It included 9 men and 3 women with a mean age of 70 ± 10 years and a mean LVEF of 50 ± 8%.

Blood tests. White blood cells count was 8.5 ± 2.5 × 10^9/l in Group A, 6.6 ± 1.5 × 10^9/l in Group B, and 8.9 ± 2.4 × 10^9/l in Group C (p = 0.050). Neutrophils count was 6.4 ± 2.6 × 10^9/l in Group A, 4.1 ± 1.3 × 10^9/l in Group B, and 7.2 ± 2.7 × 10^9/l in Group C (p = 0.016). There was no significant difference between the median C-reactive protein levels in Group A and Group B (8.9 mg/l, range 1.3 to 261.3 mg/l vs. 3.8 mg/l, range 0.3 to 8.6; p = 0.194).

Cultures. In Group A, a total of 24 patients (57%) had positive cultures. Sites with positive cultures included blood (n = 10), pre-operative wound (n = 11), and surgical wound or lead (n = 6). A single organism was identified in 20 patients and multiple organisms were identified in 4 patients. *Staphylococcus aureus* (n = 10), other *Staphylococcus* species (n = 8), *Streptococcus* species (n = 4), and other organisms (n = 5) were found.

Transesophageal echocardiogram. Twenty-two patients (52%) had a TEE. Vegetations were suspected in 12 patients. The average vegetation size was 7.5 ± 3.5 mm.

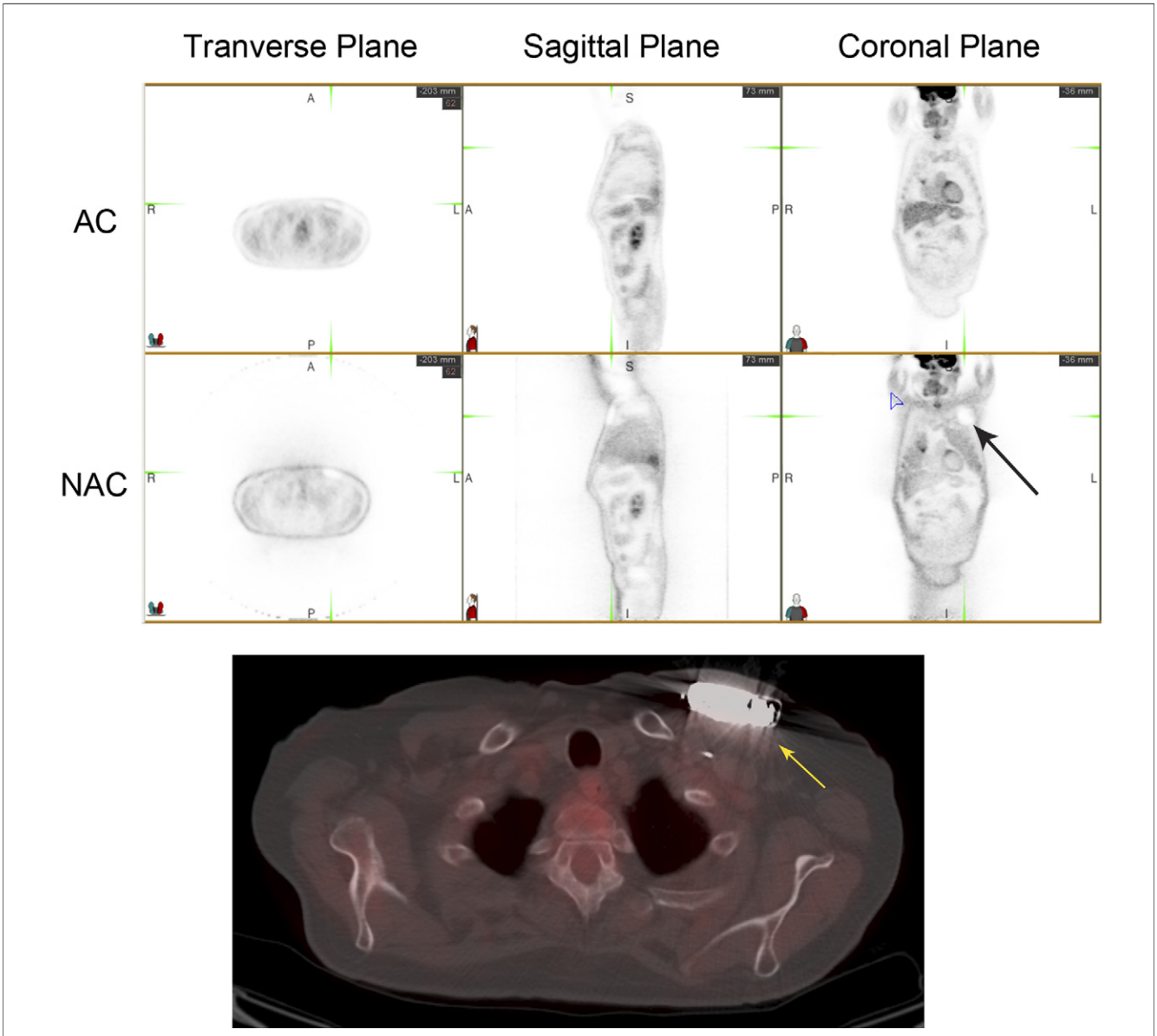

Figure 4 ^{18}F-FDG PET/CT in a Patient With Remote Cardiac Device Implantation and Lung Nodule Investigation (Group C)

(Upper panels) AC and NAC images of the ^{18}F-FDG PET in different planes shows ^{18}F-FDG uptakes of an active right lung nodule but complete absence of uptake along the cardiac device system. The **black arrow** shows the site of the generator. **(Lower panel)** No ^{18}F-FDG uptakes on a fused ^{18}F-FDG PET/CT at the level of the generator **(yellow arrow)**. Abbreviations as in Figure 1.

Table 1 Patient Characteristics

	Group A Suspected CIED Infection (n = 42)	Group B Controls Acute Phase (n = 12)	Group C Controls Chronic Phase (n = 12)	p Value
Age, yrs	62 ± 17	65 ± 8	70 ± 10	0.189
Male/female, n	28/14	11/1	9/3	0.315
LVEF, %	44 ± 17	39 ± 13	50 ± 8	0.053
CAD	14 (33)	6 (50)	6 (50)	0.478
Diabetes mellitus	11 (26)	1 (8)	2 (17)	0.388
Warfarin	18 (43)	6 (50)	7 (58)	0.730
Corticosteroids use	3 (7)	0	0	1.000
Type of device				
Pacemaker	25 (60)	6 (50)	10 (83)	0.259
Defibrillator	17 (40)	6 (50)	2 (17)	
Biventricular device	7 (17)	3 (25)	0	0.781
Number of leads	2.2 ± 0.8	2.0 ± 0.7	1.8 ± 0.5	0.123
Time since last intervention, months	11.2 (0.3–101.5)	1.3 (1.0–2.1)	24.5 (8.0–130.2)	<0.001*
Confirmed infection	35 (83)	0	0	<0.001

Values are mean ± SD, n (%), or median (minimum to maximum), unless otherwise specified. *Comparison between Group A and Group B, $p < 0.001$; comparison between Group A and Group C, $p < 0.001$; comparison between Group B and Group C, $p = 0.010$.
CAD = coronary artery disease; CIED = cardiovascular implantable electronic device; LVEF = left ventricular ejection fraction.

The vegetations were seen on the leads in 7 patients, on the valves in 2 patients, and on both in 3 patients. However, increased ^{18}F-FDG uptake in the same anatomical site was seen in only 6 patients.

^{18}F-FDG PET/CT. Higher doses of ^{18}F-FDG were used in Group C compared with Group A (370.6 ± 27.5 MBq vs. 288.8 ± 69.6 MBq) (Table 2). The calculated mean radiation dose for an ^{18}F-FDG PET/CT in the context of CIED infection was 7.0 mSv, which is less than a coronary angioplasty. In Group A, 32 of 42 patients (76%) with suspected CIED infection had a positive ^{18}F-FDG PET/CT. Abnormal uptake was visualized around the generators (n = 18), over the leads (n = 18), in the superficial skin tissue (n = 13), in the subcutaneous tissue (n = 13), and within the heart (n = 2). Figure 1 shows an example of confirmed CIED infection with a positive ^{18}F-FDG PET/CT in a patient with deep pocket infection and ^{18}F-FDG uptake seen posterior to the generator. Figure 2 shows another example of CIED infection in a patient with pocket infection as well as an infected epicardial lead. Six patients had ^{18}F-FDG uptake limited to superficial tissues without direct contact with the generator or leads, and were treated as superficial skin infection with sustained clinical improvement at 9.1 ± 6.6 months. One patient with more extensive positive ^{18}F-FDG PET/CT was treated with chronic antibiotic suppressive therapy because of significant

Table 2 ^{18}F-FDG PET/CT Results

	Group A Suspected CIED Infection (n = 42)	Group B Controls Acute Phase (n = 12)	Group C Controls Chronic Phase (n = 12)	p Value
Dose				
MBq	288.8 ± 69.6	248.0 ± 70.8	370.6 ± 27.5	<0.001
mCi	7.7 ± 1.8	7.3 ± 1.6	9.9 ± 0.9	0.002
Maximal SUV	4.4 ± 1.6	1.2 ± 1.4	0	<0.001
Qualitative visual score				
Median	2.0	0.8	0	<0.001*
Lower quartile	1.3	0.5		
Upper quartile	2.5	1.0		
Semi-quantitative ratio				
Median	2.02	1.08	0.57	<0.001†
Lower quartile	1.30	0.84	0.40	
Upper quartile	2.98	1.31	0.62	

Values are mean ± SD. *Comparison between Group A and Group B, $p < 0.001$; comparison between Group A and Group C, $p < 0.001$; comparison between Group B and Group C, $p < 0.001$. †Comparison between Group A and Group B, $p = 0.005$; comparison between Group A and Group C,$p < 0.001$; comparison between Group B and Group C, $p = 0.010$.
^{18}F-FDG PET/CT = fluorodesoxyglucose marked by fluorine-18 positron emission tomography and computed tomography; CIED = cardiovascular implantable electronic device; SUV = standardized uptake value.

comorbidities (elderly woman with severe cachexia). One patient with positive ^{18}F-FDG PET/CT but negative leukocyte scan was considered a false positive due to a Dacron pouch surrounding the device. Ten patients with negative ^{18}F-FDG PET/CT were treated with antibiotics only and none had relapsed at 12.9 ± 1.9 months (initial diagnoses = local superficial infection in 4, bacteremia in 5, and fever of unknown origin in 1).

In Group B, patients had no or mild uptake only seen at the level of the connector. Figure 3 shows an example of a patient with presence of mild residual inflammation 4 to 8 weeks post–device implantation at the level of the connector. There was no abnormal uptake in any of Group C patients. Figure 4 shows an example of a patient undergoing lung nodule investigation with remote cardiac device implantation and complete absence of ^{18}F-FDG uptake along the cardiac device system.

Qualitative visual score and semi-quantitative ratio of ^{18}F-FDG PET/CT. The median qualitative visual score was significantly higher in Group A (A = 2.0 [lower quartile = 1.3, upper quartile = 2.5] vs. B = 0.8 [lower quartile = 0.5, upper quartile = 1.0] vs. C = 0; $p < 0.001$). The median semiquantitative ratio was also significantly higher in Group A (A = 2.02 [lower quartile = 1.30, upper quartile = 2.98] vs. B = 1.08 [lower quartile = 0.84, upper quartile = 1.31] vs. C = 0.57 [lower quartile = 0.40, upper quartile = 0.62]; $p < 0.001$).

Sensitivity and specificity of ^{18}F-FDG PET/CT. On the basis of the qualitative visual score, the sensitivity of ^{18}F-FDG PET/CT for diagnosis of CIED infection in Group A was 0.886 (95% confidence interval: 0.723 to 0.963) with a specificity of 0.857 (95% confidence interval: 0.420 to 0.992). On post-hoc analysis using the semi-quantitative ratio, an ROC curve revealed an area under the curve at 0.887 ($p < 0.001$) for all 3 groups (Fig. 5). Using a ratio greater than 1.87, a specificity of 100% was achieved, meaning that all patients had confirmed CIED infections. After exclusion of acute controls (Group B), the ROC curve showed a higher area under the curve at 0.961 ($p < 0.001$) with no chronic controls (Group C) having a semi-quantitative ratio above 1.00.

Extraction. Twenty-four patients with positive ^{18}F-FDG PET/CT underwent complete extraction with excellent correlation between sites of ^{18}F-FDG uptakes and the localization of infection at the time of the extraction (0.798; $p < 0.001$). In 20 patients with confirmed deep pocket infection during the extraction, 19 patients had significant ^{18}F-FDG uptakes in the same anatomical location; 1 patient had pocket tissue induration during the extraction but no ^{18}F-FDG uptakes at that site, although the same patient also had vegetation seen on TEE and corresponding ^{18}F-FDG uptake on the lead. Finally, 4 patients underwent extraction for bacteremia and lead vegetations seen on TEE without signs of pocket infection; in these patients, the ^{18}F-FDG PET/CT revealed ^{18}F-FDG uptakes on the lead but no ^{18}F-FDG uptakes at the level of the pocket.

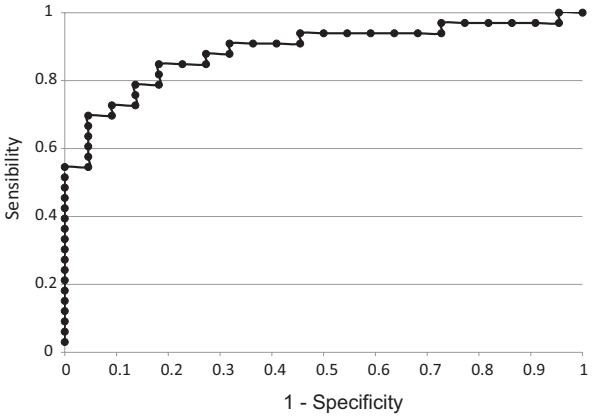

Figure 5 **Receiver-Operating Characteristic Curve for ^{18}F-FDG PET/CT Semi-Quantitative Ratio for the Diagnosis of Cardiovascular Implantable Electronic Device Infection**

The receiver-operating characteristic curve revealed an area under the curve at 0.887 ($p < 0.001$). Abbreviations as in Figure 1.

Discussion

Main findings. ^{18}F-FDG PET/CT is helpful to differentiate between an active cardiac device infection and residual normal post-operative inflammation still sometimes present 4 to 8 weeks after the operation. The ratio between maximal device count and normal lung parenchyma allows adequate differentiation between post-operative inflammation and active infection. In addition, patients with absence of ^{18}F-FDG uptakes despite an initial suspicion of CIED infection had a good outcome with initial antibiotic therapy alone, suggesting that ^{18}F-FDG PET/CT could help in risk stratification and decision management of these patients.

^{18}F-FDG PET/CT results. ^{18}F-FDG PET/CT was positive in 31 patients with confirmed CIED infection. There was only 1 false positive case related to the presence of a Dacron pouch surrounding the generator; Keidar et al. (6) previously described a similar mild ^{18}F-FDG uptake as a post-operative foreign-body inflammatory reaction. The diagnosis of CIED infection was obvious in some patients with device erosion or local signs of infection, but not in several other patients. In addition, the presence of a positive ^{18}F-FDG PET/CT combined to a more extensive ^{18}F-FDG anatomical distribution had a significant impact on the final management of these patients. Indeed, most patients with evidence of deep infection (24 of 27 patients) underwent extraction as opposed to patients with a limited superficial skin infection who were more likely to be treated with a more conservative approach and antibiotics only. This approach appears adequate because there was an excellent correlation between ^{18}F-FDG uptakes results and findings during the extraction as well as good mid-term results in the subgroup of patients treated with antibiotics only.

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The result of a negative ^{18}F-FDG PET/CT also provided useful additional information. It allowed a successful conservative management in patients with initial suspicion of CIED infection. In this subgroup of patients, 4 patients were treated successfully as a limited superficial skin infection without mid-term recurrence, 4 patients had bacteremia without evidence of device involvement and treated successfully with intravenous antibiotics without recurrence or need for lead extraction, 1 patient had bacteremia with an abdominal source identified, and 1 patient was finally diagnosed with reactive arthritis. A negative ^{18}F-FDG PET/CT probably avoided complete extraction in 6 patients.

On the basis of this information, we propose 2 algorithms incorporating the ^{18}F-FDG PET/CT in the evaluation and management of patients with either initial CIED infection suspicion (Fig. 6A) or patients with cardiac device and bacteremia or fever of unknown origin (Fig. 6B).

Recent post-implantation changes. This study provides unique information by including a new subgroup of patients with recent device intervention, as these patients were excluded from previous studies (15). As expected, a mild level of residual inflammation was present in patients with a recent intervention. However, using a semi-quantitative ratio (ratio between maximal device count and normal lung parenchyma), we were able to differentiate between residual post-operative inflammation and an active infectious process. The best combination of sensitivity and specificity was obtained using a score of 1.5.

The site of ^{18}F-FDG uptakes also appears important. In patients with a recent intervention, the site of mild ^{18}F-FDG uptakes was usually located near the junction between the leads and the connector. ^{18}F-FDG uptakes around the generator and over the leads seem to be in favor of an infectious process. Because no significant ^{18}F-FDG uptake is present several months after the last intervention, chances of a false positive after 6 months are very low. This confirms results found in the study of Ploux et al. (15).

Correlation with transesophageal echocardiogram. Out of 12 patients with suspected lead or valve vegetations noted on TEE, 6 patients also had a positive ^{18}F-FDG uptake in the same anatomic location, confirming the diagnosis of CIED infection and lead infection. In the 6 other patients without ^{18}F-FDG uptakes, it is difficult to conclude if it could be a false negative (i.e., infected vegetation without uptake), a sterile vegetation, a fibrin strand, or a localized thrombus. However, 3 patients with bacteremia and vegetation on TEE but negative ^{18}F-FDG PET/CT were successfully treated medically without long-term recurrence, and 1 patient with vegetation on TEE but negative blood culture and ^{18}F-FDG PET/CT was found to have no active infection. This favors the concept that many patients could have strands around leads without infection and that ^{18}F-FDG PET/CT could be the test of choice to confirm an active infection (17). This may well change the initial treatment strategy and may prevent unnecessary lead extractions. However, the sensitivity and specificity of this test in this subgroup of patients are unknown. Further studies are required in order to clarify the appropriate management of patients with suspected vegetation on TEE but negative ^{18}F-FDG PET/CT.

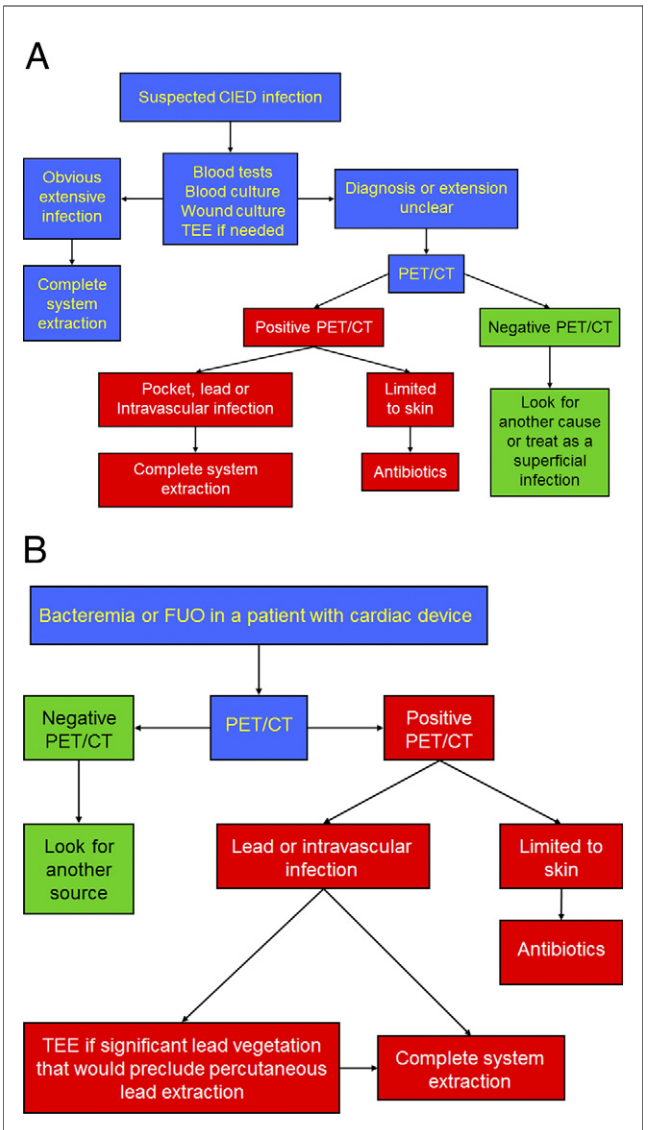

Figure 6 **Algorithms**

Proposed algorithms incorporating the ^{18}F-FDG PET/CT in the evaluation and management of patients with either initial CIED infection suspicion **(A)** or patients with cardiac device and bacteremia or fever of unknown origin (FUO) **(B)**. Abbreviations as in Figure 1.

Study limitations. The usefulness of ^{18}F-FDG PET/CT in slowly growing chronic infection is unknown. Prolonged antibiotics therapy can probably lead to a negative ^{18}F-FDG PET/CT mainly if the focus is small or antibiotics have been given for more than 1 week. The sensitivity and specificity within the first post-operative month were not evaluated in this study and are unknown, but likely lower. ^{18}F-FDG PET/CT in patients with Parsonnet pouches, Dacron pouch, or antibiotic mesh around devices have not been studied yet, but we report a case of false positive

^{18}F-FDG PET/CT in a patient with Dacron in his pocket. Leukocyte scans were not systematically performed in this study; although likely more specific, it has a lower resolution than the ^{18}F-FDG PET/CT. Longer follow-up will be required to ascertain that there is no late infection recurrence. The 2 proposed algorithms are now being tested prospectively. Although no data are available on the cost-effectiveness of this approach, it could be acceptable if it avoids unnecessary lead extractions and device re-implantations (estimated costs in Canada for a pacemaker are $30,000 and for a defibrillator are $60,000 to $80,000, while the initial ^{18}F-FDG PET/CT cost is less than $2,500 in Canada).

Conclusions

^{18}F-FDG PET/CT is useful in differentiating between cardiovascular implantable electronic device infection and recent post-implantation changes, and to assess the extension of the infectious process. Also, the absence of abnormal ^{18}F-FDG uptake among asymptomatic patients implanted with pacemaker or defibrillator for at least 6 months suggest that there is no long-term uptake post-implant, hence a low risk of false positive after such time. This imaging modality is promising for this new indication. It may guide appropriate therapy and help to limit complex and high-risk lead extractions to the more appropriate patients.

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REFERENCES

1. Uslan DZ, Sohail MR, St Sauver JL, et al. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. Arch Intern Med 2007;167:669–75.
2. Nery PB, Fernandes R, Nair GM, et al. Device-related infection among patients with pacemakers and implantable defibrillators: incidence, risk factors, and consequences. J Cardiovasc Electrophysiol 2010;21:786–90.
3. Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. J Am Coll Cardiol 2006;48:590–1.
4. Wilkoff BL, Love CJ, Byrd CL, et al. Transvenous lead extraction: Heart Rhythm Society expert consensus on facilities, training, indications, and patient management: this document was endorsed by the American Heart Association (AHA). Heart Rhythm 2009;6:1085–104.
5. Baddour LM, Epstein AE, Erickson CC, et al., American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; Council on Cardiovascular Disease in Young; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Nursing; Council on Clinical Cardiology; Interdisciplinary Council on Quality of Care; American Heart Association. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. Circulation 2010;121:458–77.
6. Keidar Z, Engel A, Hoffman A, Israel O, Nitecki S. Prosthetic vascular graft infection: the role of ^{18}F-FDG PET/CT. J Nucl Med 2007;48:1230–6.
7. Zhuang H, Duarte PS, Pourdehnad M, et al. The promising role of ^{18}F-FDG PET in detecting infected lower limb prosthesis implants. J Nucl Med 2001;42:44–8.
8. Vanquickenborne B, Maes A, Nuyts J, et al. The value of ^{18}F-FDG PET for the detection of infected hip prosthesis. Eur J Nucl Med Mol Imaging 2003;30:705–15.
9. Chen SH, Ho KC, Hsieh PH, Lee MS, Yen TC. Potential clinical role of [(18)F]FDG-PET/CT in detecting hip prosthesis infection: a study in patients undergoing two-stage revision arthroplasty with an interim spacer. Q J Nucl Med Mol Imaging 2010;54:429–35.
10. Vos FJ, Bleeker-Rovers CP, van Dijk APJ, Oyen WJG. Detection of pacemaker and lead infection with FDG-PET. Eur J Nucl Med Mol Imaging 2006;33:1245.
11. Khamaisi M, Medina A, Mazouz B, Bocher M. Imaging coronary sinus infection in pacemaker electrode with [18F]-fluorodeoxyglucose positron emission tomography. J Cardiovasc Electrophysiol 2008;19:1327–8.
12. Abikhzer G, Turpin S, Bigras JL. Infected pacemaker causing septic lung emboli detected on FDG PET/CT. J Nucl Cardiol 2010;17:514–5.
13. Turpin S, Lambert R, Poirier N. An unusual looking pacemaker infection imaged with 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging 2010;37:1438.
14. Bensimhon L, Lavergne T, Hugonnet F, et al. Whole body [(18)F]fluorodeoxyglucose positron emission tomography imaging for the diagnosis of pacemaker or implantable cardioverter defibrillator infection: a preliminary prospective study. Clin Microbiol Infect 2011;17:836–44.
15. Ploux S, Riviere A, Amraoui S, et al. Positron emission tomography in patients with suspected pacing system infections may play a critical role in difficult cases. Heart Rhythm 2011;8:1478–81.
16. Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol 2007;49:1851–9.
17. Downey BC, Juselius WE, Pandian NG, et al. Incidence and significance of pacemaker and implantable cardioverter-defibrillator lead masses discovered during transesophageal echocardiography. Pacing Clin Electrophysiol 2011;34:679–83.

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